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(54) An orally administered drug form comprising a polar bioactive agent and an adjuvant.

(57) A drug form is provided for increasing the oral absorption of polar bioactive agents such as xanthines, polyhydroxylic substances, zwitterions, polypeptides and organic anions and related chemical species by the oral administration of said polar bioactive agents in a suitable pharmaceutically accepted excipient to which has been added a hydroxyaromatic, hydroxyaryl or hydroxy aralkyl acid or salt amide or ester thereof. The hydroxy aryl or hydroxy aralkyl acid or salt amide or ester thereof is present in the drug form in quantities sufficient to be effective in enhancing the rate of oral absorption of the polar bioactive agents.

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TITLE OF THE INVENTION

AN ORALLY ADMINISTERED DRUG FORM COMPRISING
A POLAR BIOACTIVE AGENT AND AN ADJUVANT

BACKGROUND OF THE INVENTION5 Field of the Invention

The present invention relates to the oral delivery of polar bioactive agents which by this route are slowly absorbed and more especially to the enhancement of this delivery by formulations which
10 contain a hydroxyaromatic acid.

As employed in this application, the term "polar bioactive agents" refers to those therapeutic substances which, due to their polar nature, are slowly absorbed from the gastrointestinal tract and include xanthines, 5 polyhydroxylic compounds, zeitterions, polypeptides, organic anions and related chemical compounds.

DESCRIPTION OF THE PRIOR ART

It is well known to the art that a number of bioactive agents are so polar that they are only slowly 10 absorbed from the gastrointestinal tract. Consequently, these agents, on the basis of the current art, must be administered by the intravenous or intramuscular route or in excessively large oral doses in order to attain clinical efficacy. The β -lactam antibiotics and the 15 glycosidic antibiotics are two examples of bioactive agents which are slowly absorbed by the oral route. Similarly, there are a number of other polar bioactive agents such as the xanthines, antitumor agents, narcotic analgesics, agents which contain organic anions, 20 polyhydroxylic agents and polypeptides which, due to their hydrophilic nature, are also slowly absorbed from the gastrointestinal tract. The hydrophilic, polar nature of these agents precludes their rapid absorption so that even the small percentage which is absorbed is subject to a 25 long residency time in the gastrointestinal environment where both acidic and enzymatic degradation contribute to their poor bioavailability. It is therefore clear that any factor which enhances the rate of absorption will demonstrate improved clinical efficacy.

Many attempts have been made to improve the oral absorption of these polar bioactive agents. The degradation caused by the gastric acid and enzymes can be partially overcome by coating. This process in some instances can lead to some enhanced oral absorption, but in no case does it allow complete absorption. Other approaches center on the reduction of the hydrophilicity by preparing a chemical derivative which is more lipophilic. The more lipophilic derivative is more rapidly absorbed so that the residency time in the degrading gastric medium is minimized.

In spite of the numerous attempts to prepare a dosage form of these polar bioactive agents, there still exists a clear and present need for a novel method to enhance the oral absorption of polar bioactive agents. Said method would permit the oral use of a number of agents containing organic anions, polyhydroxy agents and polypeptides, and would provide an improved oral dosage form for xanthines, narcotic analgesics and a number of other agents.

SUMMARY OF THE INVENTION

Accordingly, a major object of this invention is to provide a novel class of agents which enhance the oral absorption of polar bioactive agents.

Another object is to provide a process utilizing said novel class of agents to enhance the oral absorption of polar bioactive agents.

Another object is to provide a stable drug form utilizing said novel class of agents which when administered orally will provide increased blood levels of the therapeutic agent.

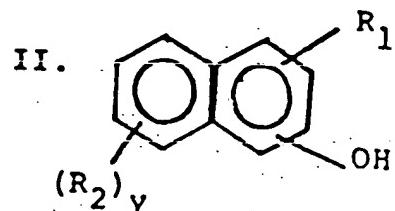
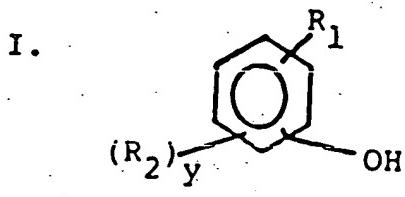
Other objects, features and advantages of the invention will be apparent to those skilled in the art from the detailed description of the invention which follows.

- 5 All of the foregoing objects are readily attained by providing a method and drug form wherein the oral absorption of polar bioactive agents is enhanced, the method comprising the steps of preparing a drug form suitable for oral delivery, and a drug form comprising an
10 effective unit dosage amount of the polar bioactive agents, a hydroxyaryl or hydroxyaralkyl acid or salt, amide or ester thereof, the latter adjuvants being present in said drug form in an amount sufficient to be effective in enhancing the rate of the oral absorption of the
15 therapeutic substance, and a suitable pharmaceutically accepted excipient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention, generally comprises the steps of preparing a drug form capable of being orally administered, wherein the drug form comprises an effective unit dosage amount of a polar bioactive agent and a hydroxyaryl or hydroxyaralkyl acid or salt, amide or ester thereof, the hydroxyaryl or hydroxyaralkyl acid or salt ester or amide thereof being present in the drug form in a sufficient quantity to be effective in enhancing the oral absorption rate and administering the drug form to warm-blooded animals. The amount of polar bioactive agent varies over a wide range, but generally any therapeutically effective unit dosage amount of the selected polar bioactive agent is used.
20
25
30

The hydroxyaryl or hydroxyaralkyl acids or their salts esters or amides thereof that are used as the adjuvants in our method and in our drug forms have the following structural formulae including the various 5 isomers possible within the formulae set forth:



wherein R₁ is a radical selected from -CO₂H,
H,

- (CH₂)_n-COOH, -CH = CH-CO₂H, -C- CO₂H;

R₃

-SO₃H, -CH₂SO₃H, X(CH₂)_nCO₂H, SO₂NHR,

PO(OH)N(OH)₂, PO(OH)OR₄ or a pharmaceutically

- 10 acceptable salt thereof wherein R₂ is the radical
-selected from OH, H, a lower alkoxy radical having 1-10
carbon atoms, a lower alkyl radical having 1-10 carbons, a
lower alkenyl radical having 2-5 carbon atoms, a lower
alkanoyl radical having 1-5 carbon atoms, a lower
15 alkanoyloxy radical having 1-5 carbon atoms, a carboxy
radical, a carbo-lower alkoxy radical having 1-5 carbon
atoms, a halo radical, a mono-, di-, or tri-halo lower
alkyl radical having 1-5 carbon atoms, an amino radical, a
mono- or di-lower alkyl amino radical having 1-5 carbon
20 atoms, a carbamyl radical, a lower mono- or di-alkyl
carbamyl radical wherein the alkyl group has 1-5 carbon
atoms, a thio radical, a lower alkyl thio radical wherein

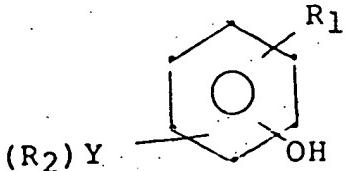
the alkyl group has 1-5 carbon atoms, a cyano radical, a lower alkyl sulfone radical wherein the alkyl group has 1-5 carbon atoms, a lower alkyl sulfoxide radical wherein the alkyl group has 1-5 carbon atoms, a nitro radical,

5 $\text{N}(\text{CN}_2)_2$, $\text{C}(\text{CN})_3$, an alkynyl radical having 2-6 carbon atoms, a cycloalkyl radical having 3-10 carbon atoms, a cycloalkenyl radical having 3-10 carbon atoms, an aryl radical including phenyl, a heteroaryl radical including thiophenyl and imadazoalyl, or heterocycloalkyl radical including morphilinyl and piperdinyl,

10 wherein R_3 is a straight or branched alkyl radical having 1-6 carbon atoms or a hydroxy radical, wherein R_4 is H or a lower alkyl radical having 1-5 carbon atoms,

15 wherein X is O or S, wherein n is an integer of 0-5, wherein y is 1 or 2, and when y is 2, both the R_2 radicals, taken together, can form a ring containing O, N or S.

20 More preferred adjuvants are those having the formula:

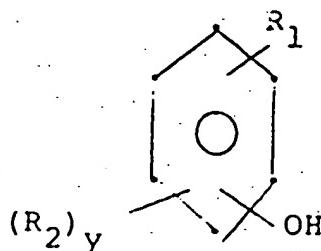


wherein R_1 is a radical selected from
 $\text{-CO}_2\text{H}$, $-(\text{CH}_2)$ -COOH , $-\text{CH}=\text{CH-CO}_2\text{H}$, $-\text{C}(\text{H})\text{-CO}_2\text{H}$,
 $-\text{SO}_3\text{H}$,
25. $-\text{CH}_2\text{SO}_3\text{H}$, $\text{O}(\text{CH}_2)\text{CO}_2\text{H}$ or a pharmaceutically acceptable salt thereof wherein R_2 is selected from OH, H, a lower alkoxy radical having 1-10 carbon atoms, a halo radical, a mono-, di-, or tri-halo lower alkyl radical wherein the alkyl group has 1-5 carbon atoms, a lower

alkyl thio radical wherein the alkyl radical has 1-5 carbon atoms, a cycloalkyl radical having 3-10 carbon atoms, or a cycloalkenyl radical having 3-10 carbon atoms and wherein

- 5 y is an integer of 1 or 2.

Highly preferred adjuvants are those having the formula:



H

wherein R_1 is CO_2H , $-(\text{CH}_2)_2\text{-COOH}$, $-\text{C}-\text{CO}_2\text{H}$, SO_3H , OH

- or a pharmaceutically acceptable salt thereof wherein R_2 10 is OH, H, a lower alkoxy radical including methoxy, ethoxy, butoxy, or octyloxy, a lower alkyl radical including methyl, isopropyl, ethyl, t-butyl, n-butyl, or t-octyl, a halo radical, or a tri-halo lower alkyl radical including trifluoromethyl, and
15 wherein y is an integer of 1 or 2.

Specific adjuvants useful in our method and drug forms for enhancing oral absorption of polar bioactive agents include salicyclic acid, resorcylic acid, and gentisic acid. Other hydroxyaryl or hydroxyaralkyl acids, 20 such as 1-hydroxy-2-naphthoic acid, naphthoresorcylic acid, ferulic acid, caffeic acid, and homovanillic acid, have similar useful adjuvant activity in our process. Such adjuvants are not considered novel per se and may be prepared by techniques known to those skilled in the art.

The amount of hydroxyaryl or hydroxyaralkyl acids or salt ester or amide thereof used in our method and drug forms may vary over a wide range; in general, the identity and the amount of the hydroxyaryl or hydroxyaralkyl acid or salt ester or amide thereof is used in connection with the drug in order to be effective in enhancing the absorption rate of the drug from the gastrointestinal compartment into the bloodstream. The effectiveness of the hydroxyaromatic acid adjuvants becomes significant at local concentration exceeding 0.01% at the absorption site. Their use at a dosage whereby their concentration at the absorption site exceeds 5% is not recommended because of the local irritating effect on the tissue.

The polar bioactive agents whose enhanced oral delivery is a subject of the present invention encompass a variety of therapeutic agents such as the xanthines, triamterene and theophylline, the antitumor agents, 5-fluoroouridinedeoxyriboside, 6-mercaptopurine-deoxyriboside, vidarabine, the narcotic analgesics, hydromorphone, cyclazine, pentazocine, bupomorphine, the compounds containing organic anions, heparin, prostaglandins and prostaglandin-like compounds, cromolyn sodium, carbenoxolone, the polyhydroxylic compounds, dopamine, dobutamine, L-dopa, α -methyldopa, the polypeptides, angiotensin antagonists, bradykinin, insulin, ACTH, enkaphaline, endorphin, somatostatin, secretin and the miscellaneous compounds such as tetracyclines, bromocriptine, lidocaine, cimetidine or any related compounds. The quantity of these polar bioactive agents necessary for preparing the drug form could vary over a wide range, but would normally be regulated by that quantity necessary to comprise the therapeutically effective dosage form.

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The following combinations of polar bioactive agents related compounds and hydroxyaryl or hydroxy aralkyl acids were given to beagle dogs by gavage. The urine was collected by catheterization and blood by venous puncture.

<u>Example</u>	<u>Polar Bioactive Agent</u>	<u>Hydroxyaryl or Hydroxyaralkyl Acid</u>
1	triamterene	sodium salicylate
2	theophylline	salicylic acid
3	5-fluoroouridinedeoxyribose	gentistic acid
5	6-mercaptopurinedeoxyribose	ferulic acid
5	vidarabine	naphthoresorcylic acid
6	hydromophone	caffeic acid
7	cyclazine	sodium salicylate
8	pentazocine	salicylic acid
10	bupomorphine	gentisic acid
10	heparin	sodium gentisate
11	15-methyl prostraglandin E ₂	sodium ferulate
12	cromolyn sodium	resorcylic acid
13	carbenoxolone	sodium gentisate
15	dopamine	salicylic acid
15	dobutamine	caffeic acid
16	l-dopa	1-hydroxy-2-naphthoic acid
17	α-methyldopa	homovanilllic acid
18	saralasin acetate	sodium salicylate
20	bradykinin	ferulic acid
20	insulin	caffeic acid
21	ACTH	sodium homovanillate
22	enkaphalin	salicylic acid
23	endorphin	sodium salicylate
25	somatostatin	gentisic acid
25	secretin	sodium ferulate
26	chlorotetracycline	salicylic acid
27	bromocriptine	caffeic acid
28	lidocaine	sodium ferulate
30	cimetidine	homovanilllic acid

The drug forms of this invention are suitably administered in oral dosage form, such as by tablet or capsule, by combining the polar bioactive agent in a therapeutic amount and the hydroxyaryl or hydroxyaralkyl acid or salt ester or amide thereof in a sufficient quantity to be effective to enhance oral delivery with an oral pharmaceutically acceptable inert carrier, such as lactose, starch (pharmaceutical grade), dicalcium phosphate, calcium sulfate, Kaolin, mannitol and powdered sugar. In order to reduce the irritation in the stomach, the preferred dose form of the hydroxyaryl or hydroxyaralkyl acid should be a pharmaceutically acceptable salt and the drug form should be designed to release the polar bioactive agent and the hydroxyaryl or hydroxyaralkyl acid salt beyond the pylorus. In addition, when required, suitable binders, lubricants, disintegrating agents, and coloring agents can also be added. Typical binders include, without limitation, starch, gelatin, sugars such as sucrose, molasses, and lactose, natural and synthetic gums, such as acacia, sodium alginate, extract of Irish moss, carboxymethylcellulose, methylcellulose, and polyvinylpyrrolidone, polyethylene glycol, ethylcellulose and waxes. Typical lubricants for use in these dosage forms can include, without limitation, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine and polyethylene glycol. Suitable disintegrators can include, without limitation, starch, methylcellulose, agar, bentonite, cellulose and wood products, alginic acid, guar gum, citris pulp, carboxymethylcellulose, and sodium lauryl sulfate. Optionally, if desired, a conventionally, pharmaceutically acceptable dye can be incorporated into oral dosage unit form, e.g., any of the standard FD & C dyes.

EXAMPLE IPreparation of Sodium 2-hydroxy-5-methoxy benzenesulfonate

- p-Methoxyphenol (12.4 g) was dissolved in chloroform (100 ml) and cooled in ice. Chlorosulfonic acid (11.6 g) was added dropwise to the stirred reaction mixture. The cooling bath was removed after the addition and stirring continued for 24 hours at room temperature. The chloroform was then evaporated off and the residue was vacuum dried to a hygroscopic light brown solid weighing 10. 20.5 g which was 2-hydroxy-5-methoxy-benzenesulfonic acid.
- NMR (CDCl_3) 3.73 (3H, s, OCH_3), 6.8-7.2 (3H, m, aromatic H), and 9.86 (2H, broad s, OH and SO_3H). IR (film) 3500-2900, 1512, 1470, 1229, 1198, 996, 938 cm^{-1} .
- The above sulfonic acid (10 g) was dissolved in water (10 ml) and poured into 75 ml of saturated sodium chloride solution. A white solid separated immediately. It was filtered and dried. Crystallization from water gave the pure sodium salt of 2-hydroxy-5-methoxy-benzenesulfonic acid (6.6 g).
- NMR (D_2O) 3.83 (3H, s, OCH_3), 7.05 and 7.33 (3H, multiplets, aromatic). IR (KBr) 3260, 1518, 1440, 1300, 1280, 1240, 1210, 1905, 1045 cm^{-1} .
- Typical preparation of enteric-coated tablets containing adjuvant.

EXAMPLE II

Typical preparation of enteric-coated tablets
continuing adjuvant.

125 mg Methyldopa Tablets

	<u>Ingredient</u>	<u>Amount per Tablet</u>
5	Methyldopa	125 mg
	Sodium 5-methoxysalicylate	250 mg
	Microcrystalline cellulose	150 mg
	Lactose	95 mg
10	Magnesium stearate	40 mg
	Total	660 mg

All ingredients except 1/4 of the magnesium stearate were mixed and the material slugged using 1/2" flat head punches. The slugs were broken up and passed 15 through a 40 mesh screen. The remaining magnesium stearate was added and mixed in. Tablets were made with 7/16" deep concave punches to a hardness of 10 Kg.

Coating:

The tablets were coated with 11 mg of pre-coat 20 and 32 mg of enteric coating according to the coating procedure described below.

Enteric Coating Procedure

Tablets or capsules were placed in a coating pan containing baffles to provide adequate tumbling. A small 25 amount of the coating solution was applied using an air sprayer and the solvents evaporated with a warm air supply

directed into the coating pan. This procedure was repeated until the desired amount of coating material was applied. The amount of coating material was determined from the weight gain of a representative group of tablets.

5 Coating Solutions:

Pre-coat: A film of hydroxypropylmethylcellulose was applied to the tablets followed by an enteric coating.

Enteric coat: A film of hydroxypropylmethyl-cellulosephthalate was applied.

10 Solutions: A 5% by weight solution of hydroxy-propylmethylcellulose and a 10% by weight solution of hydroxypropylmethylcellulosephthalate in ethanol:methylene chloride (1:1 by weight) were used as the coating solutions.

15

EXAMPLE III

In the like manner of Example II the following amount of various drugs may be incorporated into tablets using the same excipient and adjuvant and preparation technique described above:

	<u>Drug</u>	<u>Amount</u>
	hydrochlorothiazide	75 mg.
	Sinemet (carbidopa and levodopa)	50/200 mg.
5	cyclobenzaprine	10 mg
	diflunisal	250 mg.
	indomethacin	75 mg.
	methyldopa	500 mg.
	sulindac	200 mg.
10	ibuprofen	600 mg.
	naproxen	250 mg.
	phenylbutazone	100 mg.
	dexamethasone	4 mg
	prednisolone	25 mg.
15	clonidine	0.1 mg.
	propranolol	40 mg.
	diazepam	5 mg.
	chlorodiazepoxide	5 mg.
	furosemide	60 mg.
20	cephamandole	1000 mg.
	nalidixic acid	1000 mg.
	haloperidol	3 mg.
	captopril	
	timolol	

- 5 (-)-1-(cyclopropylmethyl)-
4-[3-(trifluoromethylthio)-
5H-dibenzo(a,d) cyclohepten-
5-ylidene]piperidine hydro-
chloride
- 10 N-[(S)-1-(ethoxycarbonyl)-3-
phenylpropyl]-L-alanyl-L-
proline maleate
- 15 (+)10,11-dihydro-5-methyl-5H-
dibenzo[a,d] cyclohepten-5,10-
imine oxalate
- 20 1-ethyl-6-fluoro-1,4-dihydro-4-
oxo-7-(1-piperazinyl)-3-quinol-
inecarboxylic acid
- 25 3-fluoro-D-alanine and D-4-(1-
methyl-3-oxo-1-butenylamino)-
3-isoxazolidinone sodium salt
hemihydrate
- 30 L-N-(2-oxopiperidin-6-yl-
carbonyl)-histidyl-L-thiazol-
idine-4-carboxamide
- 35 N-formimidoyl thienamycin
monohydrate
- 40 (6,7-dichloro-2-methyl-2-
phenyl-1-oxo-5-indanyloxy)
acetic acid
- The adjuvants may be chosen from the following
salts or their acids:
- 45 Sodium 5-methoxysalicylate
- 50 Sodium salicylate
- 55 Sodium homovanilate
- 60 Sodium 2,5-dihydroxybenzoate
- 65 Sodium 2,4-dihydroxybenzoate
- 70 Sodium 3,4-dihydroxymandelate
- 75 Sodium 3-methoxy-4-hydroxymandelate

- Sodium 3-methoxy-4-hydroxycinnamate
Sodium-5-methoxy-2-hydroxyphenylsulfonate
Sodium 3-methylsalicylate
Sodium 5-methylsalicylate
5 Sodium 5-tert-octylsalicylate
Sodium 3-tert-butyl-5-methylsalicylate
Sodium guaicolsulfonate
Sodium 5-bromosalicylate
Sodium 3,5-dibromosalicylate
10 Sodium 5-iodosalicylate
Sodium 3,5-diiodosalicylate
Sodium 2-hydroxyphenylacetate
Sodium 3-hydroxy-2-naphthoate
Sodium mandelate
15 Sodium phenyllataate
Sodium 2-hydroxyphenylmethanesulfonate
Sodium 5-trifluoromethyl-2-hydroxybenzoate
Sodium 4-hydroxy-3-hydroxyphenylmethanesulfonate
Sodium 3-methoxysalicylate
20 Sodium 5-octyloxysalicylate
Sodium 5-butoxysalicylate
Sodium p-hydroxyphenoxyacetate
Sodium 3,4-dihydroxyphenylacetate
Sodium 5-chlorosalicylate
25 Sodium 3,4-dihydroxycinnamate
Sodium 3,5-dihydroxybenzoate
Sodium 2-hydroxy-3-methoxybenzoate
Sodium 1-hydroxy-2-naphthoate
Sodium salicylurate
30

EXAMPLE IV

Following are also specific examples of polar bioactive agents which can be combined in equivalent ratios or previously described with any one of the hydroxyaryl or hydroxyaralkyl acids or salts, ester, or amide's thereof previously mentioned or with those specifically mentioned below

	<u>Drug</u>	<u>Adjuvant</u>
1	3,5-diamino-N-(aminoimino-methyl)-6-chloropyrazine-carboxamide (amiloride);	sodium salicylate
5	2. 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (hydrochlorothiazide);	sodium homovanillate
10	3. amiloride hydrochloride and hydrochlorothiazide (Moduretic);	2,5-dihydroxy benzoate
15	4. S- α -hydrozino-3,4-dihydroxy- α -methylbenzene-propanoic acid monohydrate (carbidopa);	sodium 5-methoxy salicylate
20	5. carbidopa and 3-hydroxy-L-tyrosine (levodopa (Sinemet));	sodium 3-methoxy salicylate
25	6. 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine (cyclobenzaprine);	2,5-dihydroxy benzoate
	7. 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (diflunisal);	sodium homovanillate
	8. 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (indomethacin);	sodium homovanillate
	9. 3-hydroxy- α -methyl-L-tyrosine (methyldopa);	sodium salicylate

	<u>Drug</u>	<u>Adjuvant</u>
10.	(Z)-5-fluoro-2-methyl-1-[{4-(methylsulfinyl)phenyl]methylen]-1H-indene-3-acetic acid (sulindac)	sodium 5-methoxy salicylate
11.	S-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol (timolol);	sodium salicylate
10	12. (-)-1-(cyclopropylmethyl)-4-[3-(trifluoromethylthio)-5H-dibenzo(a,d) cyclohepten-5-ylidene]piperidine hydrochloride	sodium salicylate
15	13. N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline maleate	sodium homovanillate
20	14. (+)10,11-dihydro-5-methyl-5H-dibenzo[a,d] cyclohepten-5,10-imine oxalate	2,5-dihydroxy benzoate
25	15. 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid	sodium 5-methoxy salicylate
30	16. 3-fluoro-D-alanine and D-4-(1-methyl-3-oxo-1-butenylamino)-3-isoxazolidinone sodium salt hemihydrate	sodium 3-methoxy salicylate
35	17. L-N-(2-oxopiperidin-6-yl-carbonyl)-histidyl-L-thiazolidine-4-carboxamide	sodium salicylate
40	18. (6,7-dichloro-2-methyl-2-phenyl-1-oxo-5-indanyloxy) acetic acid	sodium homovanillate
45	19. α-methyl-4-(2-methylpropyl)benzeneacetic acid (ibuprofen)	sodium homovanillate

	<u>Drug</u>	<u>Adjuvant</u>
20.	(+)-6-methoxy- α -methyl-2-naphthaleneacetic acid (naproxen)	sodium salicylate
5 21.	5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetic acid	sodium 5-methoxy salicylate
22.	4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone)	sodium salicylate
10 23.	9-fluoro-11 β ,17,21-trihydroxy-16 α -methyl pregn-1,4-diene-3,20-dione(dexamethasone)	sodium salicylate
24.	11 β ,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone)	sodium homovanillate
15 25.	2-(2,6-dichloroanilino)-2-imidazoline (clonidine)	2,5-dihydroxy benzoate
26.	1-(isopropylamino)-3-(1-naphthoxy)-2-propanol (propranolol)	sodium 5-methoxy salicylate
20 27.	7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam)	sodium 3-methoxy salicylate
28.	7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide (chlorodiazepoxide)	sodium salicylate
25 29.	5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid (furosemide)	2,5-dihydroxy benzoate
30 30.	1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (nalidixic acid)	sodium homovanillate
31.	4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (haloperidol)	sodium 5-methoxy salicylate
35 32.	1-(3-mercaptop-2-methyl-1-oxo-propyl)-L-proline (captopril)	sodium salicylate

As already described, the method of the present invention for enhancing the rate of absorption of polar bioactive agents orally is useful for a wide range of these particular drugs. Without limiting the broad applicability of the novel method, there is also pointed out below a number of these drugs for which the novel method is particularly useful.

3,5-diamino-N-(aminoiminomethyl)-6-chloropyrazine-carboxamide (amiloride);

10 6-chloro-3,4-dihydro-2H-1,24-benzothiadiazine-7-sulfonamide-1,1-dioxide (hydrochlorothiazide);

amiloride hydrochloride and hydrochlorothiazide (Moduretic);

15 S- α -hydrozino-3,4-dihydroxy- α -methylbenzenepropanoic acid monohydrate (carbidopa);

carbidopa and 3-hydroxy-L-tyrosine (levodopa) (Sinemet);

3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine (cyclobenzaprine);

2',4'-difluoro-4-hydroxy[1,1'-biphenyl]-3-carboxylic acid
20 (diflunisal);

1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid
(indomethacin);

3-hydroxy- α -methyl-L-tyrosine (methyldopa);

5 (Z)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)phenyl]methyl-
ene]-1H-indene-3-acetic acid (sulindac);

S-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol (timolol);

(-)-1-(cyclopropylmethyl)-4-[3-(trifluoromethylthio)-5H-dibenzo(a,d) cyclohepten-5-ylidene]piperidine hydrochloride

10 N-[(S)-1(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline maleate

(+)-10,11-dihydro-5-methyl-5H-dibenzo[a,d] cyclohepten-5,10-imine oxalate

15 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

3-fluoro-D-alanine and D-4-(1-methyl-3-oxo-1-butenylamino)-3-isoxazolidinone sodium salt hemihydrate

L-N-(2-oxopiperidine-6-ylcarbonyl)-histidyl-L-thiazolidine-4-carboxamide

(6,7-dichloro-2-methyl-2-phenyl-1-oxo-5-indanyloxy) acetic acid

α -methyl-4-(2-methylpropyl)benzeneacetic acid (ibuprofen)

(+)-6-methoxy- α -methyl-2-naphthaleneacetic acid (naproxen)

5 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetic acid

4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone)

9-fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione (dexamethasone)

11 β ,17,21-trihydroxypregna-1,4-diene-3,20-dione

10 (prednisolone)

2-(2,6-dichloroanilino)-2-imidazoline (clonidine)

1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol
(propranolol)

7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (diazepam)

7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide (chlordiazepoxide)

5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid (furosemide)

1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (nalidixic acid)

5 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (haloperidol)

1-(3-mercaptop-2-methyl-1-oxopropyl)-L-proline (captopril)

Any skilled artisan concerned with the subject matter of this invention can prepare these oral dosage forms by simply referring to the oral dosage form preparatory procedure outlined in REMINGTON'S PHARMACEUTICAL SCIENCES, Fifteenth Edision (1975), pages 1576 through 1617 inclusive.

From the foregoing description, one of ordinary skill in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to varius usages and conditions. As such, such changes and modifications are properly, equitably, ant intended to be, within the full range of equivalence of the following claims.

Rx82A

25

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CLAIMS:

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1. An orally administered drug form comprising a therapeutically effective amount of polar bioactive agent and an adjuvant comprising a hydroxyaryl or hydroxyaralkyl acid, or salt amide or ester thereof, said adjuvant being present in said drug form in sufficient amount to be effective in enhancing the oral absorption rate of said polar bioactive agent.

10

2. The drug form of Claim 1 wherein said polar bioactive agent is xanthines, anti-tumor agents, narcotic analgesics, biologically active organic anion, polyhydroxylic bioactive compounds, bioactive polypeptides or bioactive agents.

20

3. The drug form of Claim 2 wherein said xanthines is triamterene or theophylline.

25

4. The drug form of Claim 2 wherein said antitumor agent is 5-fluorouridine deoxyribose, 6-mercaptopurine deoxyribose or vidarabine.

30

5. The drug form of Claim 2 wherein said narcotic analgesic is hydromorphone, eyclazine, pentazocine or bromophenol.

35

1
6. The drug form of Claim 2 wherein
said biologically active organic anion is
5 heparin, 15-methyl prostaglandin E₂, cromolyn
sodium or carbinoxolone.

10 7. The drug form of Claim 2 wherein
said polyhydroxylic bioactive compounds is
dopamine, dobutamine, 1-dopa, or α -methyldopa.

15 8. The drug form of Claim 2 wherein
said bioactive peptides is saralasin acetate,
bradykinin, insulin, ACTH, enkaphalin, endorphin,
somatostatin or secretin.

20 9. The drug form of Claim 2 wherein
said polar bioactive agent is chlorotetracycline,
bromocriptine, lidocaine or cimetidine.

25 10. The drug form of Claim 2 wherein
said polar bioactive agent is amiloride, hydro-
chlorothiazide, moduretic, carbidopa, levodopa,
cyclobenzaprine, diflunisal, indomethacin,
methyl*dopa*, sulindac, timolol, (-)-1-(cyclo-
propylmethyl)4-/3-(trifluoromethylthio) 5H-
dibenzo(a,d)cyclohepten-5-ylidene

7

piperidine
hydrochloride, N-/7(S)-1-(ethoxycarbonyl)-3-
phenylpropyl

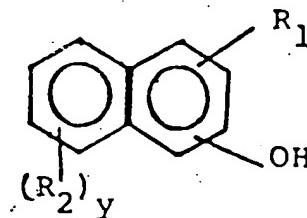
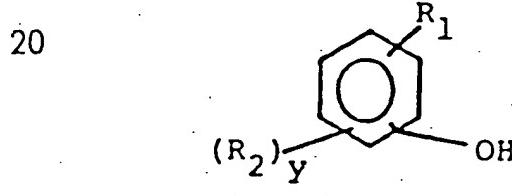
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L-alanyl-L-prolinemaleate, (+)10,11-

30

1 dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine
 oxalate, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piper-
 ziny1)-3-quinoline-carboxylic acid, 3-fluoro-D-alanine and
 5 D-4-(1-methyl-3-oxo-1-butenylamino)-3-isoxazolidinone
 sodium salt hemihydrate, L-N-(2-oxopiperidin-6-ylcarbonyl)-
 histidyl-L-thiazolidine-4-carboxamide, (6,7-dichloro-
 2-methyl-2-phenyl-1-oxo-5-indanyloxy) acetic acid,
 ibuprofen, naproxen, 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-
 10 hyrrole-2-acetic acid, phenylbutazone, dexamethasone, pred-
 nisolone, clonidine, propranolol, diazepam,
 chlorodiazepoxide, furosemide, nalidixic acid,
 haloperidol, or captopril.

15 11. The drug form of anyone of Claims 1 to
 10 wherein said adjuvant comprises

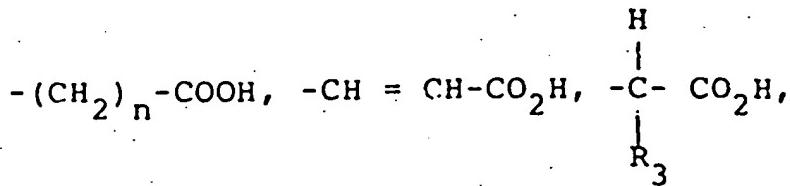


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wherein R₁ is a radical selected from -CO₂H,

30

35



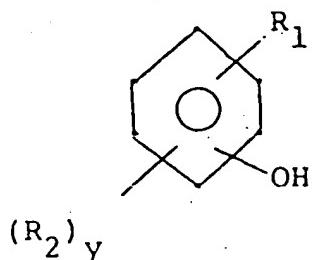
5 $-\text{SO}_3\text{H}$, $-\text{CH}_2\text{SO}_3\text{H}$, $\text{X}(\text{CH}_2)_n\text{CO}_2\text{H}$, $\text{SO}_2\text{NHR}_4^+$,

PO(OH)N(OH)_2 ,

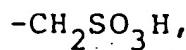
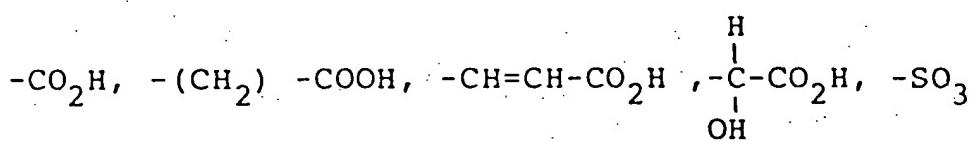
PO(OH)OR₄, or a pharmaceutically acceptable salt thereof
 10 wherein R₂ is a radical selected from OH, H, a lower alkoxy radical having 1-10 carbon atoms, a lower alkyl radical having 1-10 carbon atoms, a lower alkenyl radical having 2-5 carbon atoms, a lower alkanoyl radical having 1-5 carbon atoms, a lower alkanoyloxy radical having 1-5 carbon atoms, a carboxy radical, a carbo-lower alkoxy radical having 1-5 carbon atoms, a halo radical, a mono-, di-, or tri-halo lower alkyl radical having 1-5 carbon atoms, an amino radical, a mono- or di-lower alkyl amino radical having 1-5 carbon atoms, a carbamyl radical, a lower mono- or di-alkyl carbamyl radical wherein the alkyl group has 1-5 carbon atoms, a thio radical, a lower alkyl thio radical wherein the alkyl group has 1-5 carbon atoms, a cyano radical, a lower alkyl sulfone radical wherein the alkyl group has 1-5 carbon atoms, a lower alkyl sulfoxide radical wherein the alkyl group has 1-5 carbon atoms, a nitro radical, N(CN)₂, C(CN)₃, an alkynyl radical having 2-6 carbon atoms, a cycloalkyl radical having 3-10 carbon atoms, a cycloalkenyl radical having 3-10 carbon atoms, an aryl radical, a heteroaryl radical including thiophenyl and imadzoaryl, or a heterocycloalkyl radical,
 15 wherein R₃ is a straight or branched alkyl radical
 20
 25
 30

having 1-6 carbon atoms or a hydroxy radical,
 wherein R₄ is H or a lower alkyl radical having 1-5
 carbon atoms,
 wherein X is O or S,
 5 wherein n is an integer of 0-5,
 wherein y is 1 or 2, and
 when y is 2, both the R₂ radicals, taken together, can
 form a ring containing O, N or S.

12. The drug form of anyone of Claims 1 to 10
 10 wherein said adjuvant comprises



wherein R₁ is a radical selected from



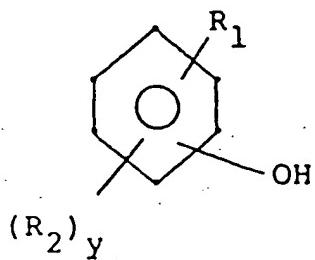
O(CH₂)₂CO₂H or a pharmaceutically acceptable salt

15 thereof

wherein R₂ is selected from OH, H, a lower alkoxy radical having 1-10 carbon atoms, a lower alkyl radical having 1-10 carbon atoms, a halo radical, a mono-, di-, or tri-halo lower alkyl radical wherein the alkyl group has 20 1-5 carbon atoms, a lower alkyl thio radical wherein the

alkyl radical has 1-5 carbon atoms, a cyloalkyl radical having 3-10 carbon atoms, or a cycloalkenyl radical having 3-10 carbon atoms and wherein y is an integer of 1 or 2.

13. The drug form of anyone of Claims 1 to 10
5 wherein said adjuvant comprises



wherein R₁ is CO₂H, (CH₂) COOH, -C(H)-CO₂^H, or
OH

SO₃H,

or a pharmaceutically acceptable salt thereof
wherein R₂ is OH, H, lower alkoxy radical, a lower alkyl
10 radical, a halo radical, or a tri-halo lower alkyl
radical, and
wherein y is an integer of 1 or 2.

14. The drug form of anyone of Claims 1 to 10
wherein said adjuvant is 5-methoxysalicylic acid, salicylic
15 acid, homovanilllic acid; 2,5-dihydroxybenzoic acid;
2,4-dihydroxybenzoic acid; 3,4-dihydroxymandelic acid;
3-methoxy-4-hydroxy-cinnamic acid; 5-methoxy-2-hydroxy-
phenylsulfonic acid; 3-methylsalicylic acid; ;
5-methylsalicylic acid; 5-tert-octylsalicylic acid; 3-tert-

butyl-6-methylsalicylic acid; 3,5-diisopropylsalicylic acid; 3-tert-butyl-5-methylsalicylic acid; guaicolsulfonic acid; 5-bromo-~~salicylic~~ acid; 3,5-dibromo-~~salicylic~~ acid; 5-iodosalicylic acid; 3,5-diiodosalicylic acid;

5 3,5-diiodosalicylic acid; 2-hydroxyphenylacetic acid; 3-hydroxy-2-naphthoic acid; mandelic acid; phenyllactic acid; 2-hydroxyphenylmethanesulfonic acid; 5-trifluoromethyl-2-hydroxybenzoic acid;

10 4-hydroxy-3-hydroxyphenylmethanesulfonic acid; 3-methoxy- salicylic acid; 5-octyloxysalicylic acid; 5-butoxy- salicylic acid; p-hydroxyphenoxyacetic acid;

15 3,4-dihydroxyphenylacetic acid; 5-chlorosalicylic acid; 3,4 dihydroxycinnamic acid; 3,5-dihydroxybenzoic acid; 2-hydroxy-3-methoxybenzoic acid; 1-hydroxy-2-naphthoic acid; salicyluric acid; or the sodium salts thereof.

15. The drug form of anyone of Claims 1 to 10 wherein the adjuvant is salicylic acid or sodium salicylate.

CLAIMS FOR AUSTRIA

1. A method for enhancing the rate of absorption of an orally administered polar bioactive agent into the bloodstream, said method comprising the steps of preparing a drug form capable of being orally absorbed, said drug form comprising a therapeutically effective dosage amount of the polar bioactive agent and an adjuvant of hydroxyaryl or hydroxyaralkyl acids or salts, amides or esters thereof said adjuvant being present in said drug form in a sufficient amount to be effective in enhancing said oral absorption rate.

2. The method of Claim 1 wherein said polar bioactive agent is xanthines, antitumor agents, narcotic analgesics, biologically active organic anion, polyhydroxyl bioactive compounds or bioactive polypeptides or bioactive agents.

3. The method of Claim 2 wherein said xanthines is triamterene or theophylline.

4. The method of Claim 2 wherein said antitumor agent is 5-fluorouridine deoxyribose, 6-mercaptopurine deoxyribose or vidarabine.

5. The method of Claim 2 wherein said narcotic analgesic is hydromorphone, cyclazine, pentazocine or bupomorphine.

6. The method of Claim 2 wherein said biologically active organic anion is heparin, 15-methyl prostaglanden E₂, cromdyn sodium or carbenoxolone.

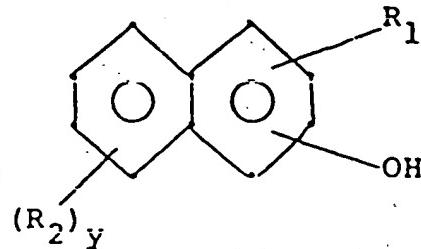
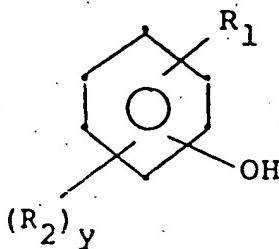
7. The method of Claim 2 wherein said polyhydroxylic bioactive compounds is dopamine, dobutamine, l-dopa, or α -methyldopa.

5. 8. The method of Claim 2 wherein said bioactive polypeptides is aralasin acetate, bradykinin, insulin, ACTH, enkaphalin, endorphin, somatostatin or secretin.

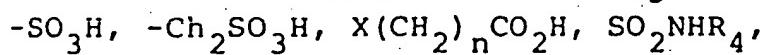
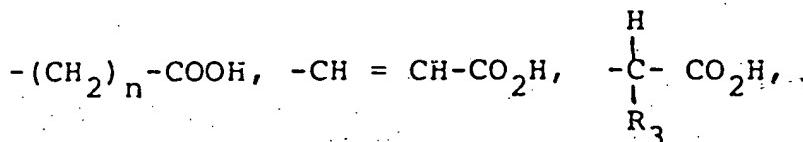
15 9. The method of Claim 2 wherein said polar bioactive agent is chlorotetracycline, bromocriptine, lidocaine or cimetidine.

10 10. The method of Claim 2 wherein said polar bioactive agent is: amiloride, hydrochlorothiazide, moduretic, carbidopa, levodopa, cyclobenzaprine, diflunisal, indomethacin, methyldopa, sulindac, timolol, (-)-1-(cyclopropylmethyl) 4-[3-(trifluoromethylthio)-5H-15 dibenzo(a,d)cyclohepten-5-ylidene]piperidine hydrochloride, N-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-L-proline maleate, (+)10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine oxalate, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid, 3-fluoro-D-alanine and D-4-(1-methyl-3-oxo-1-butenylamino)-3-isoxazolidinone sodium salt hemihydrate, L-N-(2-oxopiperidin-6-ylcarbonyl)-histidyl-L-thiazolidine-4-carboxamide, (6,7-dichloro-2-methyl-2-phenyl-1-oxo-5-indanyloxy) acetic acid, ibuprofen, naproxen, 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-hyrrole-2-acetic acid, phenylbutazone, dexamethasone, prednisolone, clonidine, propranolol, diazepam, chlorodiazepoxide, furosemide, nalidixic acid, haloperidol, and captoril.

11. The method of anyone of Claims 1 to 10 wherein said adjuvant comprises



wherein R₁ is a radical selected from -CO₂H,



5 PO(OH)N(OH)₂, PO(OH)OR₄ or a pharmaceutically acceptable salt thereof wherein R₂ is a radical selected from OH, H, a lower alkoxy radical having 1-10 carbon atoms, a lower radical having 1-10 carbon atoms, a lower alkenyl radical having 2-5 carbon atoms, a lower alkanoyl radical having 1-5 carbon atoms, a lower alkanoyloxy radical having 1-5 carbon atoms, a carboxy radical, a carbo-lower alkoxy radical having 1-5 carbon atoms, a halo radical, a mono- di-, or tri-halo lower alkyl radical having 1-5 carbon atoms, and amino radical, a mono-or di-lower alkyl amino radical having 1-5 carbon atoms, a carbamyl radical, a lower mono- or di-alkyl carbamyl radical wherein the alkyl group has 1-5 carbon atoms, a thio radical, a lower alkyl thio radical wherein the alkyl group has 1-5 carbon atoms, a cyano radical, a lower alkyl sulfone radical wherein the alkyl group has 1-5 carbon atoms, a lower alkyl sulfoxide radical wherein the

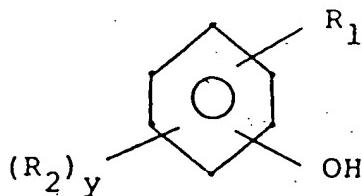
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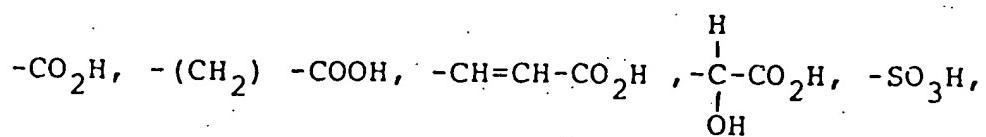
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alkyl group has 1-5 carbon atoms, a nitro radical,
 $\text{N}(\text{CN}_2)_2$, $\text{C}(\text{CN})_3$, an alkynyl radical having 2-6
 carbon atoms, a cycloalkyl radical having 3-10 carbon
 atoms, a cycloalkenyl radical having 3-10 carbon atoms, an
 5 aryl radical, a heteroaryl radical including thiophenyl and
 imadazoalyl, or a heterocycloalkyl radical,
 wherein R_3 is a straight or branched alkyl radical
 having 1-6 carbon atoms or a hydroxy radical,
 wherein R_4 is H or a lower alkyl radical having 1-5
 10 carbon atoms,
 wherein X is O or S,
 wherein n is an integer of 0-5,
 wherein y is 1 or 2, and
 when y is 2, both the R_2 radicals, taken together, can
 15 form a ring containing O, N or S.

12. The method of anyone of Claims 1 to 10
 wherein said adjuvant comprises



wherein R_1 is a radical selected from

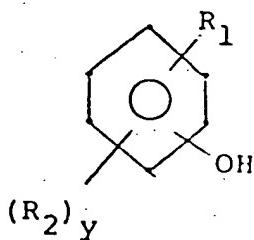


20 $-\text{CH}_2\text{SO}_3\text{H}$,

$\text{O}(\text{CH}_2)_2 \text{CO}_2\text{H}$ or a pharmaceutically acceptable salt thereof

wherein R_2 is selected from OH, H, a lower alkoxy radical having 1-10 carbon atoms, a lower alkyl radical having 5 1-10 carbon atoms, a halo radical, a mono-, di-, or tri-halo lower alkyl radical wherein the alkyl group has 1-5 carbon atoms, a lower alkyl thio radical wherein the alkyl radical has 1-5 carbon atoms, a cyloalkyl radical having 3-10 carbon atoms, or a cycloalkenyl radical having 10 3-10 carbon atoms and wherein y is an integer of 1 or 2.

13. The method of anyone of Claims 1 to 10 wherein said adjuvant comprises



wherein R_1 is CO_2H , $(\text{CH}_2)_2 \text{COOH}$, $-\text{C}(\text{H})-\text{CO}_2\text{H}$,
 $\begin{array}{c} \text{H} \\ | \\ -\text{C}-\text{SO}_3\text{H} \\ | \\ \text{OH} \end{array}$,

15 or a pharmaceutically acceptable salt thereof wherein R_2 is OH, H, a lower alkoxy radical, a lower alkyl radical, a halo radical, or a tri-halo lower alkyl radical, and

wherein y is an integer of 1 or 2.

14. The method of anyone of Claims 1 to 10
wherein said adjuvant is 5-methoxysalicylic acid,
salicylic acid, homovanillic acid, 2,5-dihydroxy-
benzoic acid; 2,4-dihydroxybenzoic acid; 3,4-di-
hydroxymandelic acid; 3-methoxy-4-hydroxycin-
namic acid; 5-methoxy-2-hydroxyphenylsulfonic acid; 3-
methylsalicylic acid; 5-methylsalicylic acid; 5-tert-
octylsalicylic acid; 3-tert-butyl-6-methylsalicylic
acid; 3,5-diisopropylsalicylic acid; 3-tert-butyl-
5-methylsalicylic acid; guaicol sulfonic acid; 5-
bromosalicylic acid; 3,5-dibromo salicylic acid; 5-
iodosalicylic acid; 3,5-diodosalicylic acid; 3,5-diiodo-
salicylic acid; 2-hydroxyphenylacetic acid; 3-hydroxy-2-
napthoic acid; mandelic acid; phenyllactic acid; 2-
hydroxyphenylmethanesulfonic acid;
5-trifluoromethyl-2-hydroxybenzoic acid; 4-hydroxy-3-
hydroxyphenylmethanesulfonic acid; 3-methoxysalicylic
acid; 5-octyloxysalicylic acid; 5-butoxysalicylic acid;
p-hydroxyphenoxyacetic acid; 3,4-dihydroxyphenylacetic
acid; 5-chlorosalicylic acid; 3,4-dihydroxycinnamic
acid; 3,5-dihydroxybenzoic acid; 2-hydroxy-3-methoxy-
benzoic acid; 1-hydroxy-2-naphthoic acid; salicyluric
acid; or the sodium salts thereof.

15. The method of anyone of Claims 1 to 10
wherein the adjuvant is salicylic acid or sodium
salicylate.



European Patent
Office

EUROPEAN SEARCH REPORT

0036145

Application number
EP 81 10 1644

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages.	Relevant to claim	
X	ROTE LISTE, 1961, Cantor, Aulendorf/Württ., DE * Page 279 "Dolorgiet", page 370, "Frenocitex", page 458, "Ilvico Merck", page 615 "Neosal", page 831 "Sanurtin", page 813 "Rulun" --	1-15	A 61 K 31/62 31/60 31/66 31/52 31/71 45/06 47/00// A 61 K 31/71 31/66 31/60 31/52 31/19)
X	ROTE LISTE, 1963, Cantor, Aulendorf/Württ., DE * Page 851 "Prednisolon Sanhelios Ampullen", "Prednisolon Sanhelios Ampullen 2 ML" --	1-15	TECHNICAL FIELDS SEARCHED (Int Cl.)
X	Dictionnaire VIDAL, 1961 Office de Vulgarisation Pharmaceutique, Paris, FR * Page 333, "Cerebrane Fournier", page 1694 "Theinol", page 96, "Antialgos" --	1-15	A 61 K 31/62 31/60 31/66 31/52 31/71 47/00 45/06
X	UNLISTED DRUGS, vol. 19, october 1967 Chatham, N.J. US * Page 138 e "Stcrnimed" --	1-15	CATEGORY OF CITED DOCUMENTS
X	UNLISTED DRUGS, vol. 14, november 1962 Chatham, N.J. US * Page 105 g "Febro-Gesic" --	1-15	X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
X	UNLISTED DRUGS, vol. 21, july 1969	1-15	& member of the same patent family. corresponding document
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	18-06-1981	BRINKMANN	



EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document, with indication, where appropriate, of relevant passages	Relevant to claim	
X	<p>FR - A - 2 293 938 (RICHTER GEDEON VEGYESZETY GYAR RT)</p> <ul style="list-style-type: none"> • Page 14, line 1 - page 15, line 9, claims 1-11 <p>& GB - A - 1 483 165</p> <p>--</p>	1-15	
X	<p>FR - A - 2 258 171 (ARIES ROBERT)</p> <ul style="list-style-type: none"> • Page 5, line 1 - page 6, line 11, claims 1-10 <p>--</p>	1-15	
X	<p>FR - A - 2 379 285 (SOCIETE D'ETUDES ET D'EXPLOITATION DE MARQUES ET BREVETS S.E.M.S.)</p> <ul style="list-style-type: none"> • Page 6, lines 1-27, claims 1-5 <p>--</p> <p>CHEMICAL ABSTRACTS, vol. 68, no. 23, 03-06-1968, page 9875, column 2, abstract 102325f Columbus, Ohio, US KONSTANTY WISNIEWSKI et al.: "Effect of insulin on the transport and the analgesic action of sodium salicylates" & Metab. Clin. Exp. 17(3), 212-17 (1965) • Abstract •</p> <p>--</p> <p>CHEMICAL ABSTRACTS, vol. 84, no. 25, 21-06-1976, page 15, column 1, abstract 173579h Columbus, Ohio, US E. BEUBLER et al.: "Methylxanthines and intestinal drug absorption" & Naunyn-Schmiedeberg's Arch. ./.</p>	1-15	TECHNICAL FIELDS SEARCHED (Int. Cl.)



EUROPEAN SEARCH REPORT

Application number

EP 01 10 1644

-2-

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.)
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
	Chatnam, N.J. US • Page 99 c "Adistop-F" --		
X	MODERN DRUG ENCYCLOPEDIA, eighth edition, The Rucben H. Donnelley Corp., 1961 New York, US • Page 279, "Coricidin" (Syrup) --	1-15	
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